MedCrave
Step into the World of Research

International Clinical Pathology Journal

Case Study

Open Access

CrossMark

Subtle brain abnormalities in congenital nephrosis syndrome: a neuropathological case study

Abstract

Background: Congenital nephrosis syndrome is caused by a dysfunctional glomerular filtration barrier. The condition is characterized by worsening proteinuria, hypoalbuminemia, and life-threatening generalized edema. Central nervous system involvement may also occur. Patients with this condition have been reported to exhibit global developmental delay, hypotonia, psychomotor debility, and rare epileptic seizures. They may also exhibit pachygyria, cortical dysplasia, cerebellar atrophy, meningeal heterotopies and hemispheric hypomyelination.

Materials and results: This report presents the case of an infant with congenital nephrosis syndrome who was unresponsive to corticosteroids. A comprehensive neuropathological examination revealed subtle brain abnormalities, including subcortical and meningeal neuronal heterotopies, as well as abrupt interruptions of the cortical layering due to abnormally penetrating meningeal vessels. These findings, which have not been reported thus far, resulted in disruption of the normal cortical organization.

Conclusions: During development, podocytes are present in the artery wall alongside other critical cells, such as pericytes. They play a crucial role in ensuring glomerular filtration in the kidneys. Defects in podocytes are a recognized cause of congenital nephrosis syndrome. Interestingly, podocytes exhibit remarkable metabolic and morphological similarities to developing neurons that target the cortex. Additionally, they are widely represented in the developing artery walls, including those in the brain during angiogenesis. Due to their pivotal role in arterial vessel development, podocyte defects may affect penetrating meningeal vessels and disrupt the corresponding cortical organization. This can result in focal abnormalities of cortical lamination. However, this defect likely occurs after neuronal cortical migration is complete because no neuronal migration defects were observed.

Keywords: congenital nephrosis syndrome, podocytes, meningeal vessel wall, BBB, cortical disruption, neuronal heterotopies

Volume 11 Issue 1 - 2026

Elvio Della Giustina, Luca Reggiani Bonetti
Division of Pathology, Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, UNIMORE, Italy

Correspondence: Elvio Della Giustina, Division of Pathology, Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, UNIMORE, Italy

Received: August 10, 2026 | **Published:** September 8, 2026

Introduction

Congenital nephrosis syndrome is a heterogeneous group of clinical and genetic disorders characterized by worsening proteinuria, hypoalbuminemia, and life-threatening generalized edema due to dysfunction of the glomerular filtration barrier. The most well-known form of the syndrome is Galloway-Mowat syndrome (GAMOS; OMIM 251300), which was first described in 1968 in two siblings presenting with congenital nephrosis, microcephaly, and a hiatal hernia.[1] Central nervous system (CNS) abnormalities, including neuronal heterotopies, pachygyria, cortical dysplasia, cerebellar atrophy, and meningeal heterotopies, have been reported in patients with congenital nephrosis syndrome, presenting with global developmental delay, hypotonia, psychomotor impairment, and epileptic seizures.[2–10] A comprehensive neuropathological study of an infant with congenital nephrosis syndrome confirmed the presence of infracortical and small meningeal heterotopies. Additionally, there were cortical changes at multiple points due to abnormally penetrating meningeal vessels. In close proximity to the penetrating vessel, the cortex lost in part the radial columnar pattern of neuronal laminae. A number of disorganized neurons accompanied the vessel wall as it penetrated the underlying white matter (WM). The cortex then appeared disorderly hypercellular, slowly recovering a not entirely normal pattern. Curious meningeal heterotopies were present at the point of the intracortical intrusion of a meningeal vessel. There was no evidence of major developmental genetic defects of cortical assembly, such as pachygyria and micropolygyria. Intracortical neuronal heterotopies are a known phenomenon associated with congenital nephrosis syndrome. However, focal disruptions of cortical layering caused by abnormal meningeal vessels have not been previously reported. By comparing this condition to Pierson syndrome, a paradigm of congenital nephrosis disease, we were able to confirm some intracortical abnormalities. However, cortical disruption by meningeal vessels, as described here, was not present in any of the extremely rare neuropathological studies of the syndrome. The causative role of podocytes is discussed and remains hypothetical. Podocytes may play a pivotal role in both the glomerular basal membrane and late cortical angiogenesis. Dysfunction of podocytes is a recognized cause of congenital nephrosis syndrome.[11,12] Additionally, they share a widespread distribution with other specialized perivascular cells, including pericytes, macrophages, and smooth muscle cells, within the walls of small arteries during development. These cells are crucial for both angiogenesis[13–15] and the formation and maintenance of a functional blood-brain barrier (BBB).[16] Therefore, we hypothesize that podocyte anomalies may be responsible for the subtle cortical abnormalities observed in this case by focally altering the normal formation and trajectories of endothelial cells in developing meningeal vessels. This may occur in the late stages of cortical angiogenesis due to the absence of major cortical dysplasias. Other regions of the brain, including the basal ganglia, cerebellum, brainstem, and spinal cord, showed no abnormalities.

Case presentation

This male newborn was born at term to healthy, unrelated parents. The delivery was spontaneous and uncomplicated. Morphometric parameters at birth were as follows: weight, 2,300 grams; length, 49 centimeters; and occipitofrontal circumference (OFC), 32 centimeters. This neonate exhibited the following dysmorphic features: a receding forehead, a broad nasal bridge, microphthalmia, sunken eyeballs, persistence of the Wachendorf membrane in her right eye, a high-arched palate, and camptodactyly of the fourth and fifth fingers in both hands. On the third day of life, he presented with early-onset nephrotic syndrome, which progressed to worsening proteinuria associated with microhematuria, cylindruria, and generalized edema. The infant did not respond to corticosteroid treatment, and his condition progressed to terminal anasarca. He died at forty-two days of age due to untreatable early-onset nephrotic syndrome. A general autopsy examination revealed isthmic aortic coarctation. Additionally, cystic dilation of the tubular lumina, atrophy, proteinaceous cysts, and diffuse mesangial proliferation were observed in the renal tissue. The final suspected diagnosis was Galloway-Mowat syndrome. The patient was neurologically poorly responsive and severely hypotonic. He required early feeding via an orogastric tube. Plantar responses were flexor, and deep tendon reflexes were barely detectable. The newborn never experienced epileptic seizures. At death, OFC values were the same as at birth, confirming moderate to severe microcephaly.

Neuropathological findings

Though this is historical material from our archive, these data emerged. The brain was fixed in a 10% formaldehyde solution for two months and weighed 377 grams afterward. The two hemispheres were cut coronally from the frontal to the occipital pole. The posterior fossa structures were cut from the rostral mesencephalon to the caudal medulla oblongata, including the cerebellum and the cervical spinal cord. There were no apparent gross abnormalities except for partially collapsed lateral ventricles, lardaceous consistency of the hemispheric white matter, and herniation of the right cerebellar tonsil. Tissue samples were taken from the frontal and parietal regions, basal ganglia, cerebellum, each level of the brainstem, and the cervical spinal cord. The fragments were embedded in paraffin and cut into 10-µm-thick sections. These sections were stained using the hematoxylin and eosin (H&E) and cresyl violet (Nissl) methods. No histostructural abnormalities were found in the basal ganglia, cerebellum, brainstem, or cervical spinal cord. The ependymal surface of the frontal horn of the lateral ventricle exhibited a few isolated nodule-like overgrowths of abnormally residual germline cells. These overgrowths are likely insufficient to define true nodular heterotopies. (Figure 1) Microscopically, the abnormalities primarily affected the fronto-parietal cortex _They consisted of neuronal heterotopies, including a peculiar type of meningeal heterotopies.

There were also several interruptions to the most superficial cortical profile, which were caused by abnormally penetrating meningeal vessels. (Figure 2) Neuronal heterotopies, which consisted of both matrix cells and pyramid-shaped neurons, were dispersed within the hemispheric WM far from the peri-paraventricular region. Some of the larger heterotopies appeared to contact the deepest cortical layers and invade the underlying WM. (Figures 3 & 4) The most peculiar abnormalities were the superficial cortical disruptions. There, the cortical surface was abruptly interrupted by the intrusion of a thin, fibrovascular meningeal strip. The incoming cortex had a normal radial and columnar organization of cortical layers, but this organization was partially lost close to the meningeal vessel penetration. Several neurons appeared alongside the walls of the penetrating vessel. The cortex appeared then disorderly hypercellular, slowly recovering an incomplete normal pattern. (Figure 5) Small, unusual meningeal heterotopies formed laterally from the point of the abnormal vessel's intrusion. Curiously, these heterotopies were almost exclusively composed of large nerve cells. No major developmental dysplasias of the cortex were observed in the vicinity of the focal abnormalities described, nor elsewhere.

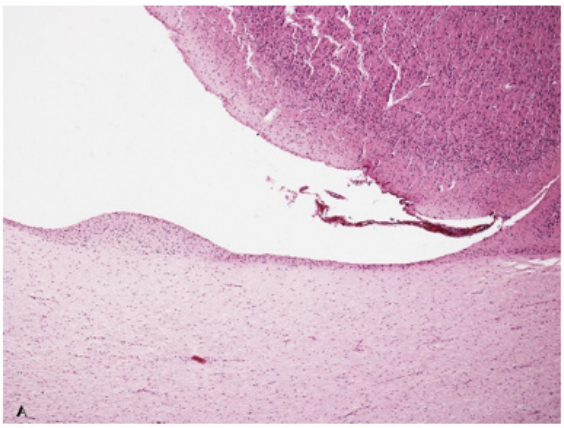

Figure 1 Some small, nodule-like overgrowths of germline cells were formed on the ependymal surface of the frontal horn of the lateral ventricle. These overgrowths are likely insufficient to define true nodular heterotopies.. H&E stain, scale bar1.5 cm, original magnification 1.25x.

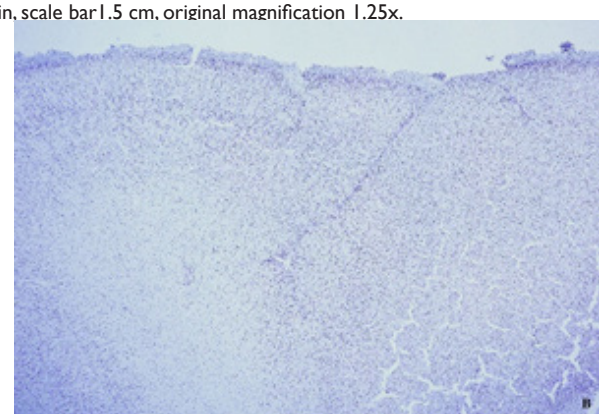

Figure 2 This is an overview of the frontoparietal region, which shows almost all of the subtle cortical abnormalities found in this case. Nissl stain, scale bar 1.5 cm, original magnification 1.25x.

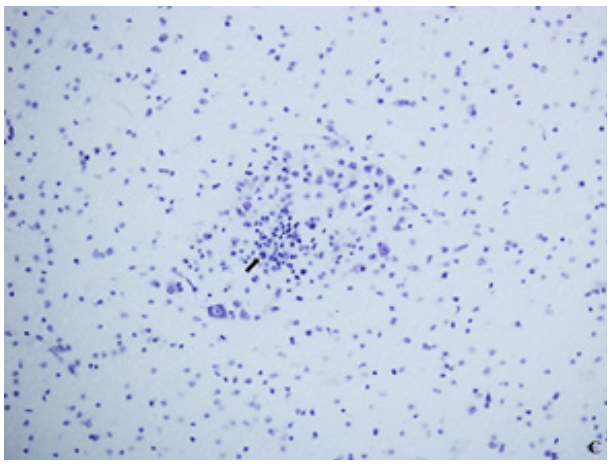

Figure 3 A few small heterotopies were observed in the frontal centrum ovale, far from the periventricular region. These heterotopies were composed by mixed medium-sized neurons, ectopic germline cells, peripheral macroneurons, and occasional polymorphonuclear cells (*black arrow*), which suggest vessel involvement. Nissl stain, scale bar 0.4 cm, original magnification 10x.

Citation: Giustina ED, Bonetti LR. Subtle brain abnormalities in congenital nephrosis syndrome: a neuropathological case study. *Int Clin Pathol J.* 2026;11(1):40–44. DOI: 10.15406/icpjl.2026.11.00226

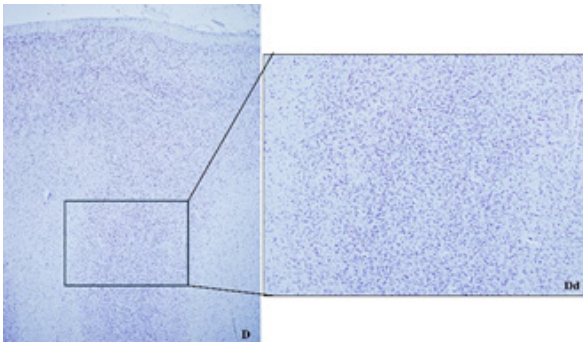

Figure 4 Some large neuronal heterotopies developed so close to the cortex that they appeared to extend its depth (Panel **D**; Nissl stain, scale bar 1.5 cm, original magnification 1.25). These heterotopies were composed of many glial cells and mixed small- and medium-sized neurons without any form of organization (Panel **De**; Nissl stain, scale bar 1.3 cm, original magnification 4x).

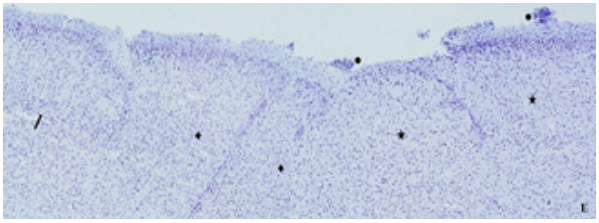

Figure 5 A detailed overview of subtle cortical abnormalitiesis provided. The following are highlighted: a normal layered, radially organized cortex preceding the abnormally penetrating vessels (*black arrow*); a partial loss of the radial columnar organization and lamination of cortical neurons approaching the abnormal vessel (*black diamonds*); a completely disorganized cortex following the abnormal penetrating vessel (*black stars*); curious meningeal heterotopies (*black balls*). Nissl stain, scale bar 1.3 cm, original magnification 4x.

Discussion

Congenital nephrosis syndrome is a clinically and genetically heterogeneous group of disorders caused by dysfunction of the glomerular filtration barrier. Brain abnormalities have been reported as well, including microcephaly, pachygyria with glioneural heterotopies in the meninges, cortical dysplasia, hypomyelination, ventriculomegaly, an immature appearance of the inferior olivary nuclei, and atrophy of the granular layer of the cerebellum.[2–8] Patients with this condition present neurologically with developmental delay, hypotonia, psychomotor insufficiency, and epilepsy, which is often untreatable.[9–10]

Glomerular podocytes are essential for forming a normal kidney filtration barrier. Similarly, they are also essential for forming the BBB in the brain.[11] The glomerular basement membrane (GBM) allows endothelial cells to anchor on one side and podocytes to anchor on the other. Podocytes have basal, apical, and lateral "hot spots", which are held together by actin filaments, as well as their own Golgi apparatus and endoplasmic reticulum (ER). Podocytes adhere to the GBM through transmembrane receptors, such as integrins (integrin α3), which are receptors for laminins, particularly laminin β2 (the product of the gene LAMB2). The integrin α3-laminin β2 bond allows podocytes to anchor to the basement membrane. The podocyte apical "hot spot" contains podocyclin, a transmembrane O-glycosylated protein that maintains the pedicles and prevents their retraction. Additionally, the podocyte cytoskeleton is rich in microtubules and intermediate filaments, while the pedicles possess abundant actin microfilaments. This complex machinery includes the nucleus, ribonucleic acid (RNA), ER, the Golgi apparatus, ribosomes, and mitochondria. It must operate under adequate quality control, largely represented by the mammalian target of rapamycin (mTOR) system. The result is the dynamic cytoarchitecture of podocytes, which enables them to respond plastically to multiple environmental stimuli. Nephrin family proteins, especially Neph1, play an additional active role in this process, including cell-to-cell adhesion and synapse formation. Experimentally, nephrins are expressed in the developing vertebrate brain, particularly in dendrites and synapses.[12] Nephrin activity integrates with CD2-associated protein (CD2AP) to regulate the actin cytoskeleton through continuous, dynamic remodeling.[13] The integration of CD2AP into the P13K/AKT survival pathway confirms the involvement of the mTOR system.[14] Mitochondria, on the other hand, supply energy through oxidative phosphorylation. Additionally, mitochondria interact with apoptotic factors such as OSGEP and TP53RK. Knocking down these factors experimentally increases apoptosis by elevating caspase-3 activity.[15] Interestingly, neurons exhibit many similarities to glomerular podocytes. Podocyte pedicles closely resemble the lamellipodia of neuronal growth cones. Furthermore, both continuously remodel their actin to target the appropriate locations in kidney and brain tissue, respectively.

Congenital nephrosis syndrome is a genetic disorder. At the time, the only genetic investigation available for this historical patient was fetal karyotyping, which resulted in a 46, XY diagnosis. Interestingly, functional genetic anomalies have been identified in patients with congenital nephrosis syndrome. One example is a dysfunctional KEOPS complex (kinase, endopeptidase, and other proteins of small size). The KEOPS complex comprises four subunits: LAGE3, OSGEP, TP53RK, and TPRKB. These subunits, especially OSGEP and TP53RK, play a role in the accuracy and efficiency of intracellular signals from tRNAs to ER and ribosomes. This process, also regulates energy metabolism and protein synthesis/autophagy.[14,15] A peculiar phenotype-genotype correlation has been linked to loss-of-function mutations in the WDR73 gene. These mutations result in postnatal microcephaly, severe intellectual disability, nephrotic syndrome, and severe atrophy of the innermost granule layer of the cerebellum.[16,17] Mutations in the LAMB2 gene cause Pierson syndrome.[18–20] As mentioned above, the gene's product, laminin β2, forms a bond with integrin α3 that ensures the functional stability of the GBM. Laminin β2 is also expressed at the neuromuscular junction and in the intraocular muscles, lens, and retina. This explains the complex ocular abnormalities and muscular hypotonia present in Pierson syndrome patients. It may also be valuable in addressing the hypotonia and movement disorder present in our patient. A thorough review of the literature revealed very few neuropathological studies in patients with Pierson syndrome. Hiser et al.[20] reported cortical hypercellularity and neuronal disorganization in the hippocampi and dentate nuclei.[20] Interestingly, previous reports have highlighted focal disruption of the pial basement membrane, meningeal neuronal ectopies, and altered distribution of Cajal-Retzius cells.[21,22] These findings are valuable because the focal cortical abnormalities observed in our patient are similar to those described in rare patients with Pierson syndrome. Notably, these abnormalities are distributed in a focal manner alongside large areas of normal cortical morphology and organization. Additionally, we clearly demonstrate that the normal radial columnar organization of the adjacent cortex is altered due to the penetrating meningeal vessel. Thereafter, the cortex does not immediately recover a normal assembly. Instead, it displays coarse hypercellularity. These additional findings in our patient have never been observed in the few previous reports. Thus, they can contribute to our understanding of the pathogenetic mechanisms involved in the cortex of congenital nephrosis syndrome. Obviously, however, a diagnosis of Pierson syndrome cannot be formally accepted for our patient.

Citation: Giustina ED, Bonetti LR. Subtle brain abnormalities in congenital nephrosis syndrome: a neuropathological case study. *Int Clin Pathol J.* 2026;11(1):40–44. DOI: 10.15406/icpjl.2026.11.00226

The features of the concomitant small meningeal heterotopies in our case are unusual. They are essentially formed by medium-sized neurons with strong chromatin positivity in the Nissl stain. Most glioneural clusters in meningeal spaces actually show mixed cell dispersion rather than a strict concentration of neurons. Since these clusters are very close to the cortical surface, one might wonder if they are abnormal Retzius-Cajal cells, as has been suggested in Pierson syndrome.[21,22] This raises questions about the possibility of focal cortical abnormalities involving other important organizers of the developing cortex, particularly the reelin-disabled-1 (Dab-1) genes. Dysfunctional reelin-Dab-1 genes generally cause major cortical abnormalities, including various forms of lissencephaly and holoprosencephaly, during development. However, minor focal defects may cause subtle cortical alterations if they occur after the cortex is formed. Notably, the absence of any signs of tissue reaction confirms the developmental, nonlesional origin of the cortical abnormalities in our case.

Conclusions

Like other brain vascular cells, such as pericytes and smooth muscle cells, podocytes are closely associated with endothelial cells. This promotes prenatal human brain angiogenesis[15] and ensures BBB integrity.[11] In the developing brain, they have the same functional machinery as in the renal glomerulus.[23–26] Notably, mural cells, including podocytes, pericytes, and smooth muscle cells, promote endothelial trajectories during angiogenesis development.[23] Defects in mural cells, especially podocytes, can result in incorrect endothelial trajectories, causing abnormal vessel pathway development, including at the meningeal-cortical boundary. The focal superficial corticovascular abnormalities observed in this case may be related to similar alterations in small meningeal vessels and their role in BBB integrity. There is still much uncertainty about the direct causative role of the altered gliopial membrane. However, the glio-pial membrane behaves like a barrier, and meningeal vessels contribute to its formation and function.In conclusion, this case demonstrates that neuropathological examinations of the brains of young patients who died of congenital nephrotic syndrome can reveal unexpected, subtle cortical changes that help us understand some unusual pathogenic mechanisms. Additionally, the findings in this case may contribute to the understanding of known congenital nephroses, such as Pierson syndrome.

Ethics statement

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. Our institution does not require ethical approval for reporting individual cases or case series.

Acknowledgments

None.

Conflicts of interest

The authors declare that they have no potential conflicts of interest to disclose.

Funding

None.

References

1. Galloway WH, Mowat AP. Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. *J Med Genet.* 1968;5(4):319–321.
2. Robain O, Deonna T. Pachygyria and congenital nephrosis disorder of migration and neuronal orientation. *Acta Neuropathol.* 1983;60:137–141.
3. Palm L, Hägerstrand I, Kristoffersson U, et al. Nephrosis and disturbances of neuronal migration in male siblings—a new hereditary disorder? *Arch Dis Child.* 1986;61(6):545–548.
4. Roos RA, Maaswinkel-Mooy PD, van der Loo EM, et al. Congenital microcephaly, infantile spasms, psychomotor retardation, and nephrotic syndrome in two sibs. *Eur J Pediatr.* 1987;146(5):532–536.
5. Kozlowski PB, Sher JH, Nicastri AD, et al. Brain morphology in the Galloway syndrome. *Clin Neuropathol.* 1989;8(2):85–91.
6. Cooperstone BG, Friedman A, Kaplan BS. Galloway-Mowat syndrome of abnormal gyral patterns and glomerulopathy. *Am J Med Genet.* 1993;47(2):250–254.
7. Kucharczuk K, de Giorgi AM, Golden J, et al. Additional findings in Galloway-Mowat syndrome. *Pediatr Nephrol.* 2000;14(5):406–409.
8. Keith J, Fabian VA, Walsh P, et al. Neuropathological homology in true Galloway-Mowat syndrome. *J Child Neurol.* 2011;26(4):510–517.
9. Nishikawa M, Ichiyama T, Hayashi T, et al. A case of early myoclonic encephalopathy with the congenital nephrotic syndrome. *Brain Dev.* 1997;19(2):144–147.
10. Pezzella M, Yeghiazaryan NS, Veggiotti P, et al. Galloway-Mowat syndrome: an early-onset progressive encephalopathy with intractable epilepsy associated to renal impairment. Two novel cases and review of literature. *Seizure.* 2010;19(2):132–135.
11. Daneman R, Zhou L, Kebede AA, et al. Pericytes are required for blood-brain barrier integrity during embryogenesis. *Nature.* 2010;468(7323):562–566.
12. Neumann-Haefelin E, Kramer-Zucker A, Slanchev K, et al. A model organism approach: defining the role of Neph proteins as regulators of neuron and kidney morphogenesis. *Hum Mol Genet.* 2010;19(12):2347–2359.
13. Machuca E, Benoit G, Antignac C. Genetics of nephrotic syndrome: connecting molecular genetics to podocyte physiology. *Hum Mol Genet.* 2009;18(R2):R185–R194.
14. Lin PY, Tseng MH, Zenker M, et al. Galloway-Mowat syndrome in Taiwan: *OSGEP* mutation and unique clinical phenotype. *Orphanet J Rare Dis.* 2018;13(1):226.
15. Braun DA, Rao J, Mollet G, et al. Mutations in the evolutionarily highly conserved KEOPS complex genes cause nephrotic syndrome with microcephaly. *Nat Genet.* 2017;49(10):1529–1538.
16. Jinks RN, Puffenberger EG, Baple E, et al. Recessive nephrocerebellar syndrome on the Galloway-Mowat syndrome spectrum is caused by homozygous protein-truncating mutations of WDR73. *Brain.* 2015;138(Pt 8):2173–2190.
17. Jiang C, Gai N, Zou, et al. WDR73 missense mutation causes infantile onset intellectual disability and cerebellar hypoplasia in a consanguineous family. *Clin Chim Acta.* 2017;464:24–29.
18. Pierson M, Cordier J, Hervouuet F, et al. An unusual congenital and familial congenital malformative combination involving the eye and kidney. *J Genet Hum.* 1963;12:184–213.
19. Funk SD, Lin MH, Miner JH. Alport syndrome and Pierson syndrome: diseases of the glomerular basement membrane. *Matrix Biol.* 2018;71–72:250–261.

20. Hiser W, Thirumala V, Wang J, et al. Pierson syndrome in an infant with congenital nephrotic syndrome and unique brain pathology. *Kidney Int Rep*. 2020;5(12):2371–2374.

21. Cagan M, Cohen AH, Matejas V, et al. A milder variant of Pierson syndrome. *Pediatr Nephrol*. 2008;23(2):323–327.

22. Chen YM, Kikkawa Y, Miner JH. A missense *LAMB2* mutation causes congenital nephrotic syndrome by impairing laminin secretion. *J Am Soc Nephrol*. 2011;22(5):849–858.

23. Crouch EE, Bhaduri A, Andrews MG, et al. Ensembles of endothelial and mural cells promote angiogenesis in prenatal human brain. *Cell*. 2022;185(20):3753–3769.

24. Blain J, Dylewski J. Regulation of the actin cytoskeleton in podocytes. *Cells*. 2020;9(7):1700.

25. Tu YC, Shu HP, Sun LL, et al. The physiopathologic roles of calcium signaling in podocytes. *Front Biosci*. 2023;28(10):240.

26. McLone DG, Naidich TP. Developmental morphology of the subarachnoid space, brain vasculature and contiguous structures, and the cause of the Chiari II malformation. *AJNR Am J Neuroradiol*. 1992;13(2):463–482.

Citation: Giustina ED, Bonetti LR. Subtle brain abnormalities in congenital nephrosis syndrome: a neuropathological case study. *Int Clin Pathol J*. 2026;11(1):40–44. DOI: 10.15406/icpjl.2026.11.00226